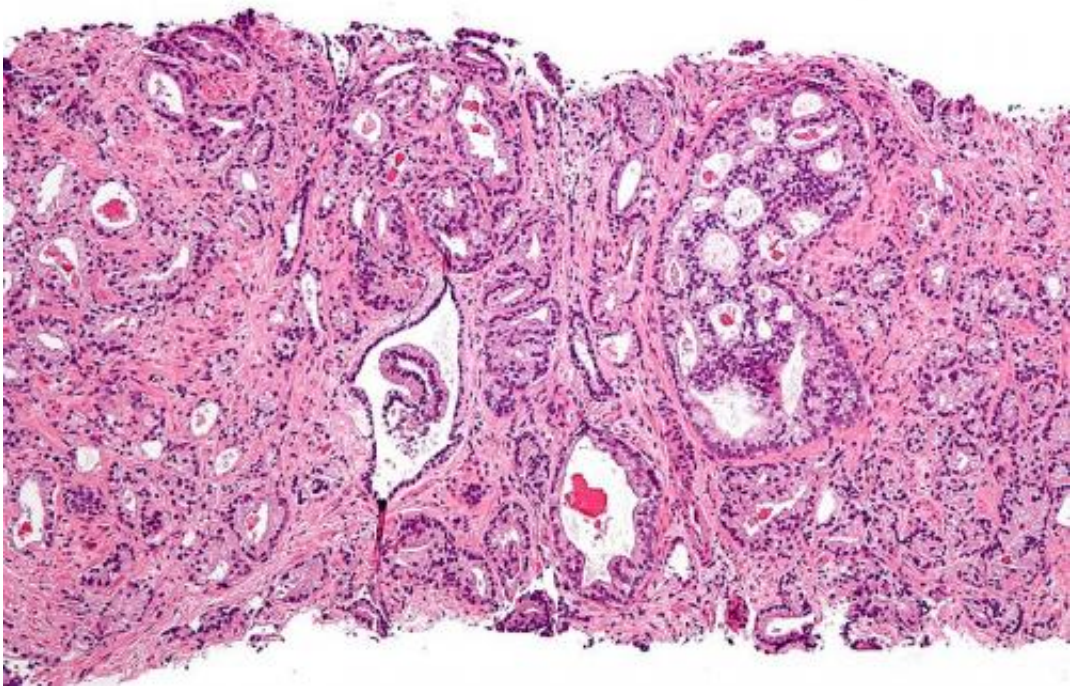
Breast cancer drug set to transform prostate cancer treatment

September 20 2020



Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

A drug used to treat breast and ovarian cancer can extend the lives of some men with prostate cancer and should become a new standard treatment for the disease, concludes a major trial which is set to change clinical practice.

Final results from the trial showed that olaparib—a pioneering type of

drug called a PARP inhibitor and the first ever cancer drug to target an inherited genetic fault—can be used successfully to treat prostate cancers with a weakness in their ability to repair damaged DNA.

The innovative drug was more effective than the modern hormone treatments abiraterone and enzalutamide at slowing down the growth and spread of prostate cancer in patients with advanced disease.

Prior results from the PROfound trial published earlier this year led to olaparib's approval by the US Food and Drug Administration (FDA) - making it one of the first genetically targeted drugs available for prostate cancer.

The trial had already reported an improvement in disease development and outcome for this group of men with DNA repair faults in their tumours—but the final results published at this stage offer a longer follow-up and conclusively demonstrate an improvement in survival for men who were given olaparib.

The PROfound trial studied 387 men with advanced prostate cancer who had defects in one or more of 15 DNA repair genes. It was funded by AstraZeneca (LSE/STO/NYSE: AZN) and co-led by The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust, alongside international collaborators including Northwestern University in Chicago, US.

Scientists at The Institute of Cancer Research (ICR) were the first to discover how olaparib could be targeted at tumours with faults in their ability to repair DNA. They now expect the concluding results from the PROfound trial—presented at the European Society for Medical Oncology today (Sunday) and published in the journal The *New England Journal of Medicine* at the same time—to pave the way for regulatory approval of olaparib in prostate cancer in Europe and in the UK.

Men whose tumours had genetic changes were assigned to two groups: one group for those with changes in BRCA1, BRCA2 or ATM, and another group for men with genetic changes in any other of the DNA repair genes studied. Men were then randomly assigned to olaparib or standard hormone therapy.

DNA damage is the basic cause of cancer—but it is also a key weakness of cancer that can be exploited, since cancer cells need to be able to repair their own DNA too.

In the final analysis of data from the PROfound trial, researchers found that olaparib blocked prostate cancer growth more effectively than the modern targeted hormone treatments abiraterone and enzalutamide in men with faulty DNA repair genes.

Patients with genetic alterations in the DNA repair genes BRCA1, BRCA2 or ATM who received olaparib had a median overall survival of 19.1 months, compared with 14.7 months for those on targeted hormone treatments. Meanwhile, patients with genetic alterations in any other of the DNA repair genes studied had an overall survival of 14.1 months with olaparib or 11.5 months with the targeted hormonal drugs.

During the trial, patients were allowed to 'cross over' - meaning that they were able to switch treatments and start taking the experimental treatment, olaparib, once their disease progressed. Overall, 66 percent of men who received the targeted hormone treatments—86 out of 131—crossed over to receive olaparib. Researchers analysed the impact on survival of crossing over from targeted hormone treatments and found that those who crossed over to olaparib were less likely to die sooner.

Thanks to the trial's results, researchers now hope to see olaparib approved in the UK once it gains approval from the European Medicines

Agency (EMA) and NICE—so that it can benefit men with advanced prostate cancer with faults in the BRCA1, BRCA2 or ATM genes who have been previously treated with modern targeted hormone treatments like abiraterone or enzalutamide.

There were trends that favoured the use of olaparib in men with DNA repair faults other than BRCA or ATM, but the data is not definitive. Next, researchers will be studying new drug combinations which could make olaparib more effective and help men with prostate cancer and faulty DNA repair genes live even longer.

Study co-leader Professor Johann de Bono, Professor of Experimental Cancer Medicine at The Institute of Cancer Research, London, and Consultant Medical Oncologist at The Royal Marsden NHS Foundation Trust, said:

"I'm confident that our results will transform prostate cancer treatment—hopefully very soon. We have shown that olaparib, a drug already approved for use in breast and ovarian cancer, can extend the lives of men with advanced prostate who have defects in the genes BRCA1, BRCA2 or ATM and who have been treated with enzalutamide or abiraterone.

"The FDA has already approved olaparib for prostate cancer in the US and I hope that the final results of our trial will bring the authorisation of this innovative drug to Europe and the UK as soon as possible. This will enable more men with the disease to take advantage of this targeted treatment so that they can have more precious time with their loved ones."

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"I'm really excited to see the genetically targeted drug olaparib making such a difference to men with prostate cancer. One of the benefits of this innovative drug is that it has far fewer side effects than chemotherapy, as it can target an Achilles heel in prostate cancers instead of also attacking healthy cells in the body.

"Olaparib is the perfect example of a smarter, kinder personalised therapy for patients—and it's great that it has been an advance led here in the UK, including pioneering ICR science and practice-changing clinical trials like this.

"The next step for our researchers is to study new treatment combinations that can take us a step further and help us prevent or overcome drug resistance—the central aim of our new Centre for Cancer Drug Discovery."

More information: Maha Hussain et al, Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer, *New England Journal of Medicine* (2020). dx.doi.org/10.1056/NEJMoa2022485

Provided by Institute of Cancer Research